Connecting via Winsock to STN

Welcome to STN International! Enter x:x

LOGINID:SSSPTA1642BJF

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * * * * * * Welcome to STN International * * * * * * * * * *

NEWS 1		Web Page URLs for STN Seminar Schedule - N. America
NEWS 2		"Ask CAS" for self-help around the clock
NEWS 3	JAN 17	Pre-1988 INPI data added to MARPAT
NEWS 4	FEB 21	STN AnaVist, Version 1.1, lets you share your STN AnaVist visualization results
NEWS 5	FEB 22	The IPC thesaurus added to additional patent databases on STN
NEWS 6	FEB 22	Updates in EPFULL; IPC 8 enhancements added
NEWS 7	FEB 27	New STN AnaVist pricing effective March 1, 2006
NEWS 8	MAR 03	Updates in PATDPA; addition of IPC 8 data without attributes
NEWS 9	MAR 22	EMBASE is now updated on a daily basis
NEWS 10	APR 03	New IPC 8 fields and IPC thesaurus added to PATDPAFULL
NEWS 11	APR 03	Bibliographic data updates resume; new IPC 8 fields and IPC thesaurus added in PCTFULL
NEWS 12	APR 04	STN AnaVist $500 visualization usage credit offered
NEWS 13	APR 12	LINSPEC, learning database for INSPEC, reloaded and enhanced
NEWS 14	APR 12	Improved structure highlighting in FQHIT and QHIT display in MARPAT
NEWS 15	APR 12	Derwent World Patents Index to be reloaded and enhanced during second quarter; strategies may be affected
NEWS 16	MAY 10	CA/CAplus enhanced with 1900-1906 U.S. patent records
NEWS 17	MAY 11	KOREAPAT updates resume
NEWS 18	MAY 19	Derwent World Patents Index to be reloaded and enhanced
NEWS 19	MAY 30	IPC 8 Rolled-up Core codes added to CA/CAplus and USPATFULL/USPAT2
NEWS 20	MAY 30	The F-Term thesaurus is now available in CA/CAplus
NEWS 21	JUN 02	The first reclassification of IPC codes now complete in INPADOC

NEWS EXPRESS FEBRUARY 15 CURRENT VERSION FOR WINDOWS IS V8.01a, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 19 DECEMBER 2005. V8.0 AND V8.01 USERS CAN OBTAIN THE UPGRADE TO V8.01a AT http://download.cas.org/express/v8.0-Discover/

NEWS HOURS	STN Operating Hours Plus Help Desk Availability
NEWS LOGIN	Welcome Banner and News Items
NEWS IPC8	For general information regarding STN implementation of IPC 8
NEWS X25	X.25 communication option no longer available after June 2006

Enter NEWS followed by the item number or name to see news on that specific topic.

* * * * * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * * *

```
FILE 'HOME' ENTERED AT 14:36:36 ON 13 JUN 2006

=> file reg
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.21       0.21

FILE 'REGISTRY' ENTERED AT 14:36:47 ON 13 JUN 2006
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2006 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:   12 JUN 2006  HIGHEST RN 887497-01-0
DICTIONARY FILE UPDATES:  12 JUN 2006  HIGHEST RN 887497-01-0

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH January 6, 2006

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

**********************************************************************
*                                                                    *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added,    *
* effective March 20, 2005.  A new display format, IDERL, is now     *
* available and contains the CA role and document type information.  *
*                                                                    *
**********************************************************************

Structure search iteration limits have been increased.  See HELP SLIMITS
for details.

REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document.  For information
on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

=> E "RM2"/CN 25
E1            1     RM-ACID/CN
E2            1     RM189/CN
E3            0 --> RM2/CN
E4            1     RM38/CN
E5            1     RM60 HOMOPOLYMER/CN
E6            1     RM7/CN
E7            1     RM711/CN
E8            1     RM715/CN
E9            1     RM721/CN
E10           1     RM723/CN
E11           1     RM80/CN
E12           1     RM801FW/CN
E13           2     RMA 1/CN
E14           1     RMA 1 (FLUX)/CN
E15           1     RMA 1 (RUBBER)/CN
E16           1     RMA 101/CN
E17           1     RMA 150M/CN
E18           1     RMA 1X/CN
E19           1     RMA 2/CN
```

```
E20           1      RMA 300M/CN
E21           1      RMA 325/CN
E22           1      RMA 390DH3/CN
E23           1      RMA 4/CN
E24           1      RMA 400/CN
E25           1      RMA 450M/CN

=> E "RM-2"/CN 25
E1            1      RM LUTE/CN
E2            1      RM PROTEIN (BACILLUS THURINGIENSIS ENTOMOCIDUS STRAIN LBIT-113
PLASMID PUIBI-1)/CN
E3            0 --> RM-2/CN
E4            1      RM-ACID/CN
E5            1      RM189/CN
E6            1      RM38/CN
E7            1      RM60 HOMOPOLYMER/CN
E8            1      RM7/CN
E9            1      RM711/CN
E10           1      RM715/CN
E11           1      RM721/CN
E12           1      RM723/CN
E13           1      RM80/CN
E14           1      RM801FW/CN
E15           2      RMA 1/CN
E16           1      RMA 1 (FLUX)/CN
E17           1      RMA 1 (RUBBER)/CN
E18           1      RMA 101/CN
E19           1      RMA 150M/CN
E20           1      RMA 1X/CN
E21           1      RMA 2/CN
E22           1      RMA 300M/CN
E23           1      RMA 325/CN
E24           1      RMA 390DH3/CN
E25           1      RMA 4/CN

=> file caplus
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                   ENTRY    SESSION
FULL ESTIMATED COST                                0.44       0.65

FILE 'CAPLUS' ENTERED AT 14:37:36 ON 13 JUN 2006
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2006 AMERICAN CHEMICAL SOCIETY (ACS)
```



```
FILE COVERS 1907 - 13 Jun 2006  VOL 144 ISS 25
FILE LAST UPDATED: 12 Jun 2006  (20060612/ED)

Effective October 17, 2005, revised CAS Information Use Policies apply.
They are available for your review at:

http://www.cas.org/infopolicy.html

=> s us 20050221397/pn
```

```
L1            1 US 20050221397/PN
                (US2005221397/PN)

=> sel rn
E1 THROUGH E1 ASSIGNED

=> file reg
COST IN U.S. DOLLARS                        SINCE FILE      TOTAL
                                               ENTRY    SESSION
FULL ESTIMATED COST                             2.49       3.14

FILE 'REGISTRY' ENTERED AT 14:37:55 ON 13 JUN 2006
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2006 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:   12 JUN 2006  HIGHEST RN 887497-01-0
DICTIONARY FILE UPDATES:  12 JUN 2006  HIGHEST RN 887497-01-0

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH January 6, 2006

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

*************************************************************************
*                                                                       *
* The CA roles and document type information have been removed from     *
* the IDE default display format and the ED field has been added,       *
* effective March 20, 2005.  A new display format, IDERL, is now        *
* available and contains the CA role and document type information.     *
*                                                                       *
*************************************************************************

Structure search iteration limits have been increased.  See HELP SLIMITS
for details.

REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document.  For information
on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

=> s e1
L2            1 850223-38-0/BI
                (850223-38-0/RN)

=> d ibib
'IBIB' IS NOT A VALID FORMAT FOR FILE 'REGISTRY'

The following are valid formats:

Substance information can be displayed by requesting individual
fields or predefined formats.  The predefined substance formats
are:  (RN = CAS Registry Number)

REG     - RN
SAM     - Index Name, MF, and structure - no RN
FIDE    - All substance data, except sequence data
IDE     - FIDE, but only 50 names
```

SQIDE - IDE, plus sequence data
SQIDE3 - Same as SQIDE, but 3-letter amino acid codes are used
SQD   - Protein sequence data, includes RN
SQD3   - Same as SQD, but 3-letter amino acid codes are used
SQN   - Protein sequence name information, includes RN

CALC   - Table of calculated properties
EPROP - Table of experimental properties
PROP   - EPROP and CALC

Any CA File format may be combined with any substance format to obtain CA references citing the substance. The substance formats must be cited first. The CA File predefined formats are:

ABS -- Abstract
APPS -- Application and Priority Information
BIB -- CA Accession Number, plus Bibliographic Data
CAN -- CA Accession Number
CBIB -- CA Accession Number, plus Bibliographic Data (compressed)
IND -- Index Data
IPC -- International Patent Classification
PATS -- PI, SO
STD -- BIB, IPC, and NCL

IABS -- ABS, indented, with text labels
IBIB -- BIB, indented, with text labels
ISTD -- STD format, indented

OBIB -------- AN, plus Bibliographic Data (original)
OIBIB ------- OBIB, indented with text labels

SBIB -------- BIB, no citations
SIBIB ------- IBIB, no citations

The ALL format gives FIDE BIB ABS IND RE, plus sequence data when it is available.
The MAX format is the same as ALL.
The IALL format is the same as ALL with BIB ABS and IND indented, with text labels.

For additional information, please consult the following help messages:

HELP DFIELDS -- To see a complete list of individual display fields.
HELP FORMATS -- To see detailed descriptions of the predefined formats.
ENTER DISPLAY FORMAT (IDE):end

=> d 1

L2   ANSWER 1 OF 1 REGISTRY COPYRIGHT 2006 ACS on STN
RN   850223-38-0 REGISTRY
ED   Entered STN: 11 May 2005
CN   β-D-Galactopyranose, O-2-(acetylamino)-2-deoxy-β-D-
     galactopyranosyl-(1→4)-O-[N-acetyl-α-neuraminosyl-
     (2→3)]-O-β-D-galactopyranosyl-(1→3)-O-[N-acetyl-α-
     neuraminosyl-(2→6)]-O-2-(acetylamino)-2-deoxy-β-D-
     glucopyranosyl-(1→3)- (9CI) (CA INDEX NAME)
FS   STEREOSEARCH
MF   C50 H82 N4 O37
SR   CA
LC   STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.

/ Structure 1 in file .gra /

/ Structure 2 in file .gra /

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> file caplus
COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION
FULL ESTIMATED COST | 2.34 | 5.48

FILE 'CAPLUS' ENTERED AT 14:38:27 ON 13 JUN 2006
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 13 Jun 2006 VOL 144 ISS 25
FILE LAST UPDATED: 12 Jun 2006 (20060612/ED)

Effective October 17, 2005, revised CAS Information Use Policies apply.
They are available for your review at:

http://www.cas.org/infopolicy.html

=> d his

(FILE 'HOME' ENTERED AT 14:36:36 ON 13 JUN 2006)

FILE 'REGISTRY' ENTERED AT 14:36:47 ON 13 JUN 2006
E "RM2"/CN 25
E "RM-2"/CN 25

FILE 'CAPLUS' ENTERED AT 14:37:36 ON 13 JUN 2006
L1 1 S US 20050221397/PN
SEL RN

FILE 'REGISTRY' ENTERED AT 14:37:55 ON 13 JUN 2006
L2 1 S E1

FILE 'CAPLUS' ENTERED AT 14:38:27 ON 13 JUN 2006

=> s l2
L3 2 L2

=> d ibib 1-2

L3 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:1078089 CAPLUS
DOCUMENT NUMBER: 143:344596
TITLE: Rm2 antigen (beta1,4-galnac-disialyl-lc4) as prostate cancer-associated antigen
INVENTOR(S): Saito, Seiichi
PATENT ASSIGNEE(S): Northern Advancement Center for Science & Technology, S. Korea
SOURCE: U.S. Pat. Appl. Publ., 13 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005221397	A1	20051006	US 2004-812357	20040330
WO 2005098434	A2	20051020	WO 2005-US10221	20050325

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2004-812357 A 20040330

L3 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:373084 CAPLUS
DOCUMENT NUMBER: 142:408646
TITLE: RM2 antigen (β1,4-GalNAc-disialyl-Lc4) as a new marker for prostate cancer
AUTHOR(S): Saito, Seiichi; Egawa, Shin; Endoh, Mareyuki; Ueno, Seiji; Ito, Akihiro; Numahata, Kenji; Satoh, Makoto; Kuwao, Sadahito; Baba, Shiro; Hakomori, Senitiroh; Arai, Yoichi
CORPORATE SOURCE: Department of Urology, Tohoku University Graduate School of Medicine, Sendai, Japan
SOURCE: International Journal of Cancer (2005), 115(1), 105-113
CODEN: IJCNAW; ISSN: 0020-7136
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> file pctfull

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	3.20	8.68

FILE 'PCTFULL' ENTERED AT 14:39:42 ON 13 JUN 2006
COPYRIGHT (C) 2006 Univentio

FILE LAST UPDATED: 13 JUN 2006 <20060613/UP>
MOST RECENT UPDATE WEEK: 200623 <200623/EW>
FILE COVERS 1978 TO DATE

>>> IMAGES ARE AVAILABLE ONLINE AND FOR EMAIL-PRINTS <<<

```
>>> NEW IPC8 DATA AND FUNCTIONALITY NOW AVAILABLE IN THIS FILE.
    SEE
    http://www.stn-international.de/stndatabases/details/ipc-reform.html >>>

>>> FOR CHANGES IN PCTFULL PLEASE SEE HELP CHANGE
    (last updated April 10, 2006) <<<

=> s RM2
L4          397 RM2

=> s antibod?
L5        88553 ANTIBOD?

=> s l5 and l4
L6           95 L5 AND L4

=> s cancer? or tumor? or neoplas?
          78950 CANCER?
          65926 TUMOR?
          22900 NEOPLAS?
L7        98312 CANCER? OR TUMOR? OR NEOPLAS?

=> s l6 and l7
L8           67 L6 AND L7

=> s prostate and l8
          24530 PROSTATE
            421 PROSTATES
          24544 PROSTATE
                (PROSTATE OR PROSTATES)
L9           23 PROSTATE AND L8

=> s l9 not py>2002
         408573 PY>2002
L10           8 L9 NOT PY>2002

=> d ibib 1-8

L10    ANSWER 1 OF 8      PCTFULL   COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER:         2002056022 PCTFULL  ED 20020725  EW 200229
TITLE (ENGLISH):          DIAGNOSTIC TUMOR MARKERS, DRUG SCREENING FOR
                          TUMORIGENESIS INHIBITION, AND COMPOSITIONS AND
                          METHODS FOR TREATMENT OF CANCER
TITLE (FRENCH):           MARQUEURS TUMORAUX DE DIAGNOSTIC, ANALYSE DE
                          MEDICAMENTS POUR L'INHIBITION DE LA
                          TUMORIGENESE, ET COMPOSITIONS ET PROCEDES POUR
                          LE TRAITEMENT DU CANCER
INVENTOR(S):              BAMDAD, Cynthia, C., 142 Church Street, Newton, MA
                          02458, US;
                          BAMDAD, R., Shoshana, 142 Church Street, Newton, MA
                          02458, US
PATENT ASSIGNEE(S):       MINERVA BIOTECHNOLOGIES CORPORATION, 142 Church Street,
                          Newton, MA 02458, US [US, US]
AGENT:                    POMIANEK, Michael, J.$, Wolf, Greenfield & Sacks, P.C.,
                          600 Atlantic Avenue, Boston, MA 02210$, US
LANGUAGE OF FILING:       English
LANGUAGE OF PUBL.:        English
DOCUMENT TYPE:            Patent
PATENT INFORMATION:

                          NUMBER             KIND     DATE
                          ---------------------------------
                          WO 2002056022        A2 20020718
DESIGNATED STATES
      W:                  AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR
```

CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID
IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD
MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI
SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW

RW (ARIPO): GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW

RW (EAPO): AM AZ BY KG KZ MD RU TJ TM

RW (EPO): AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR

RW (OAPI): BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG

APPLICATION INFO.: WO 2001-US44782 A 20011127

PRIORITY INFO.: US 2000-60/253,361 20001127
US 2000-60/255,370 20001213
US 2000-60/256,027 20001215
US 2000-60/258,157 20001222
US 2001-60/259,615 20010103
US 2001-60/260,186 20010105
US 2001-60/266,169 20010202
US 2001-60/266,929 20010206
US 2001-60/278,093 20010323
US 2001-60/289,444 20010507
US 2001-60/294,887 20010531
US 2001-60/298,272 20010614

L10 ANSWER 2 OF 8 PCTFULL COPYRIGHT 2006 Univentio on STN

ACCESSION NUMBER: 2001042786 PCTFULL ED 20020827

TITLE (ENGLISH): SYSTEM FOR CELL BASED SCREENING : CELL SPREADING

TITLE (FRENCH): SYSTEME DE CRIBLAGE A BASE DE CELLULES

INVENTOR(S): SAMMAK, Paul;
DUENSING, Thomas, D.;
RUBIN, Richard

PATENT ASSIGNEE(S): CELLOMICS, INC.;
SAMMAK, Paul;
DUENSING, Thomas, D.;
RUBIN, Richard

DOCUMENT TYPE: Patent

PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2001042786	A2	20010614

DESIGNATED STATES

W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW GH GM KE LS MW MZ SD SL SZ TZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG

APPLICATION INFO.: WO 2000-US33308 A 20001208

PRIORITY INFO.: US 1999-60/170,087 19991209

L10 ANSWER 3 OF 8 PCTFULL COPYRIGHT 2006 Univentio on STN

ACCESSION NUMBER: 2001000247 PCTFULL ED 20020828

TITLE (ENGLISH): PEPTIDE-LIPID CONJUGATES, LIPOSOMES AND LIPOSOMAL DRUG DELIVERY

TITLE (FRENCH): CONJUGUES PEPTIDES-LIPIDES, LIPOSOMES ET APPORT DE MEDICAMENTS LIPOSOMIQUES

INVENTOR(S): MEERS, Paul;
PAK, Charles;
ALI, Shaukat;
JANOFF, Andrew;
FRANKLIN, J., Craig;
ERUKULLA, Ravi;
CABRAL-LILLY, Donna;
AHL, Patrick

PATENT ASSIGNEE(S): THE LIPOSOME COMPANY, INC.
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2001000247	A1	20010104

DESIGNATED STATES
W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ
DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS
JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN
MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR
TT TZ UA UG UZ VN YU ZA ZW GH GM KE LS MW MZ SD SL SZ
TZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK
ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM
GA GN GW ML MR NE SN TD TG
APPLICATION INFO.: WO 2000-US16248 A 20000613
PRIORITY INFO.: US 1999-09/343,650 19990629

L10 ANSWER 4 OF 8 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 2000072686 PCTFULL ED 20020515
TITLE (ENGLISH): REGULATION OF SYSTEMIC IMMUNE RESPONSES UTILIZING CYTOKINES AND ANTIGENS
TITLE (FRENCH): REGULATION DE LA REPONSE IMMUNITAIRE SYSTEMIQUE A L'AIDE DE CYTOKINES ET D'ANTIGENES
INVENTOR(S): HARDY, Steve;
DRANOFF, GlennRP : NAKAMURA, Dean
PATENT ASSIGNEE(S): CELL GENESYS, INC.
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2000072686	A1	20001207

DESIGNATED STATES
W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ
DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS
JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN
MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR
TT TZ UA UG UZ VN YU ZA ZW GH GM KE LS MW MZ SD SL SZ
TZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK
ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM
GA GN GW ML MR NE SN TD TG
APPLICATION INFO.: WO 2000-US15190 A 20000602
PRIORITY INFO.: US 1999-09/324,707 19990602

L10 ANSWER 5 OF 8 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 2000057899 PCTFULL ED 20020515
TITLE (ENGLISH): THROMBOSPONDIN-2 AND USES THEREOF
TITLE (FRENCH): LA THROMBOSPONDINE-2 ET SES UTILISATIONS
INVENTOR(S): DETMAR, Michael;
STREIT, Michael
PATENT ASSIGNEE(S): THE GENERAL HOSPITAL CORPORATION;
DETMAR, Michael;
STREIT, Michael
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2000057899	A1	20001005

DESIGNATED STATES
W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ
DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS
JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN
MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT

TZ UA UG US UZ VN YU ZA ZW GH GM KE LS MW SD SL SZ TZ
UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES
FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA
GN GW ML MR NE SN TD TG

APPLICATION INFO.: WO 2000-US7835 A 20000324
PRIORITY INFO.: US 1999-60/127,221 19990331

L10 ANSWER 6 OF 8 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 2000029433 PCTFULL ED 20020515
TITLE (ENGLISH): 12-25-KDA BACTERIAL PROTEINS AND THEIR 116-58 KDA POLYMERS FOR USE E.G. IN ANTI-TUMOR VACCINES
TITLE (FRENCH): PRODUIT
INVENTOR(S): KISLITCHKINE, Nikolay
PATENT ASSIGNEE(S): TOLIN AS;
JONES, Elizabeth, Louise;
KISLITCHKINE, Nikolay
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2000029433	A2	20000525

DESIGNATED STATES
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE
DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE
KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX
NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA
UG US UZ VN YU ZA ZW GH GM KE LS MW SD SL SZ TZ UG ZW
AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR
GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN GW
ML MR NE SN TD TG

APPLICATION INFO.: WO 1999-GB3852 A 19991118
PRIORITY INFO.: RU 1998-98120511 19981118
GB 1999-9908663.9 19990415

L10 ANSWER 7 OF 8 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 1997033908 PCTFULL ED 20020514
TITLE (ENGLISH): LYTIC PEPTIDES
TITLE (FRENCH): PEPTIDES LYTIQUES
INVENTOR(S): RIVETT, Donald, Edward;
HUDSON, Peter, John;
WERKMEISTER, Jerome, Anthony
PATENT ASSIGNEE(S): COMMONWEALTH SCIENTIFIC AND INDUSTRIAL RESEARCH ORGANISATION;
RIVETT, Donald, Edward;
HUDSON, Peter, John;
WERKMEISTER, Jerome, Anthony
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9733908	A1	19970918

DESIGNATED STATES
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE
ES FI GB GE GH HU IL IS JP KE KG KP KR KZ LC LK LR LS
LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG
SI SK TJ TM TR TT UA UG US UZ VN YU GH KE LS MW SD SZ
UG AM AZ BY KG KZ MD RU TJ TM AT BE CH DE DK ES FI FR
GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN ML
MR NE SN TD TG

APPLICATION INFO.: WO 1997-AU160 A 19970313
PRIORITY INFO.: AU 1996-PN 8614 19960313

L10 ANSWER 8 OF 8 PCTFULL COPYRIGHT 2006 Univentio on STN

ACCESSION NUMBER: 1995019169 PCTFULL ED 20020514
TITLE (ENGLISH): TREATMENT OF PLATELET DERIVED GROWTH FACTOR RELATED DISORDERS SUCH AS CANCERS USING INHIBITORS OF PLATELET DERIVED GROWTH RECEPTOR
TITLE (FRENCH): TRAITEMENT DE TROUBLES LIES AU FACTEUR MITOGENIQUE PLAQUETTAIRE TELS QUE LES CANCER, UTILISANT DES INHIBITEURS DU RECEPTEUR DE FACTEUR MITOGENIQUE PLAQUETTAIRE
INVENTOR(S): HIRTH, Klaus, Peter;
SCHWARTZ, Donna, Pruess;
MANN, Elaina;
SHAWVER, Laura, Kay;
KERI, Gyorgy;
SZEKELY, Istvan;
BAJOR, Tamas;
HAIMICHAEL, Janis;
ORFI, Laszlo;
LEVITZKI, Alex;
GAZIT, Aviv;
ULLRICH, Axel;
LAMMERS, Reiner;
KABBINAVAR, Fairooz, F.;
SLAMON, Dennis, J.;
TANG, Cho, Peng
PATENT ASSIGNEE(S): SUGEN, INC.;
BIOSIGNAL LTD.;
YISSUM RESEARCH DEVELOPMENT COMPANY OF THE HEBREW UNIVERSITY OF JERUSALEM;
MAX-PLANCK-GESELLSCHAFT ZUR FORDERUNG DER WISSENSCHAFTEN E.V.;
REGENTS OF THE UNIVERSITY OF CALIFORNIA
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9519169	A2	19950720

DESIGNATED STATES
W: AM AT AU BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE HU JP KE KG KP KR KZ LK LR LT LU LV MD MG MN MW MX NL NO NZ PL PT RO RU SD SE SI SK TJ TT UA UZ VN KE MW SD SZ AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN ML MR NE SN TD TG
APPLICATION INFO.: WO 1995-US363 A 19950106
PRIORITY INFO.: US 1994-8/179,570 19940107

=> d kwic 1

L10 ANSWER 1 OF 8 PCTFULL COPYRIGHT 2006 Univentio on STN
TIEN DIAGNOSTIC TUMOR MARKERS, DRUG SCREENING FOR TUMORIGENESIS INHIBITION, AND COMPOSITIONS AND METHODS FOR TREATMENT OF CANCER
TIFR MARQUEURS TUMORAUX DE DIAGNOSTIC, ANALYSE DE MEDICAMENTS POUR L'INHIBITION DE LA TUMORIGENESE, ET COMPOSITIONS ET PROCEDES POUR LE TRAITEMENT DU CANCER
ABEN . . . a series of compositions, methods, kits, articles and species associated primarily with the diagnosis and/or treatment of cell proliferation, specifically cancer. Cell proliferation associated with aberrant expression of MUCI is particularly focused upon. Mechanisms associated with MUCI cell proliferation are discussed.
ABFR . . . de procedes, de trousses, d'articles et d'especes associes principalement au diagnostic et/ou au traitement de la proliferation cellulaire, notamment du cancer. L'invention concerne en particulier la proliferation cellulaire associee a l'expression

aberrante de MUC1, ainsi que des mecanismes associes a la. . .

DETD DIAGNOSTIC TUMOR MARKERS, DRUG SCREENING FOR TUMORIGENESIS INHIBITION, AND COMPOSITIONS AND METHODS FOR TREATMENT OF CANCER

Related Applications

This non-provisional application claims the benefit under Title 35, U.S.C.

Field of the Invention

The invention relates to assays using shed cell surface receptor interchain binding regions and cleavage products for cancer diagnosis, and for the evaluation of cancer treatment and using the portion of the receptor that remains on the cell as a molecular target for cancer therapeutics.

. . .

of the Invention

Many of the biomolecular interactions that promote turnorigenesis involve cell surface proteins that mediate both intra- and intercellular signaling. Tumor markers are proteins on the surface of a cell that are exclusively expressed, over-expressed or show an altered expression pattern as a result of transformation to a neoplastic state. The surface concentration of certain tumor markers has been correlated to the progression of cancer. For example, the interaction between the cell surface receptor aVP3 and the cell adhesion molecule vitronectin has been implicated in angiogenesis. . .

Integrins and cancer. Curr Opin Cell Biol, 1996, 8(5): 724-730; Vailhe B, Ronot X, Tracqui P, Usson Y, Tracqui L: In vitro angiogenesis is. . .

Cell surface receptors, that have been linked to cancer, make up an important class of therapeutic targets. Many pharmaceutical companies are actively involved in screening drug libraries for compounds that bind to and block these cell surface receptors. For example, an important drug used to treat breast cancer is Herceptin (Pegram M, Lipton A, Hayes D, Webber B, Baselga J, Tripathy D, Baly D, Baughman S, Twaddell T, Glaspy J, Slamon D: Phase II study of receptor-enbanced chemosensitivity using recombinant humanized anti-p 1 8 5 Her2/neu monoclonal antibody plus cisplatin, in patients with Her2/neu-overexpressing metastatic breast cancer refractory to chemotherapy treatment, J Clin Oncol, 1998, 16(8): 2659-267 1). This drug binds to and blocks HER2/neu (Ross J, Fletcher J: review, The Her2/neu oncogene in breast cancer.

. . .

for therapy. Stem Cells, 1998, 16(6): 413-428) which is a cell surface receptor that is over-expressed on 30% of breast tumors.

. . .

myeloma cells and is induced by dexamethasone. Blood, 1999, 93(4): 1287-1298), is especially interesting since it is

aberrantly expressed on many human tumors, including 80% of breast tumors, and on a significant percentage of prostate, lung, ovarian, colorectal and perhaps brain, cancers.

. . .

epithelium, MUC I is clustered at, the apical border and is not expressed over other portions of the cell. However, in tumor cells, the receptor is homogeneously over-expressed over the entire cell surface (Kufe D., Inghirami G., Abe M., Hayes D, Justi-Wheeler H, Schlom J: Differential reactivity of a novel monoclonal antibody (DF3) with human malignant versus benign breast tumors. Hybridoma, 1984, 3.

223-232), rather than just at the apical border. It is also known that women with breast cancer have elevated levels of shed MUC 1 receptor in their blood stream. Extracellular portions of the MUC I receptor are cleaved. . . least one enzyme, and released into the blood stream. Levels of shed MUC I receptor in serum are measured to track breast cancer patients for recurrence. However, the method is too variable and insensitive to be used as a general diagnostic.

Until now, the mechanistic link between the MUC I receptor and tumorigenesis has not been understood. Attempts to correlate the number of repeat units, which varies from person to person, and susceptibility to cancer failed. Investigations of a possible connection, between glycosylation of the MUCl receptor and cancer, produced conflicting results. Importantly, until now, a fimctional figand(s) for the extracellular portion of the MUC 1 receptor has not been identified.

Absent an understanding of the mechanism of the MUC I receptor, and how it triggers tumorigenesis, it has not been possible to design or identify therapeutics'that interfere with the disease-associated ftinction of this receptor. Indeed, currently there. . .

The present invention describes discoveries that elucidate critical aspects of the mechanism by which WC I triggers cell proliferation and tumorigenesis. These discoveries provide novel molecular targets for drug screening assays which the inventors have used to identify compounds that inhibit the WC. . .

. . .

of the Invention

The present invention provides a variety of kits, methods, compositions, peptide species and articles associated with cell proliferation, specifically cancer. The invention involves primarily techniques and components for the diagnosis and treatment of cancer.

Another method of the invention involves treating a subject having cancer or 3o being at risk for developing cancer, the method comprises administering to the subject an

agent that reduces cleavage of a cell surface receptor.

Another method of the invention for treating a subject having cancer or at risk for developing cancer comprises administering to the subject an agent that reduces cleavage of a cell surface receptor interchain binding region from the cell.

comprises determining an amount of cleavage of a cell surface receptor interchain binding region from a cell surface, and evaluating indication of cancer or potential for cancer based upon the determining step.

determining a site of cleavage of a cell surface receptor in a sample from a subject, and evaluating an indication of cancer or potential for cancer based upon the determining step.

Another method of the invention involves treating a subject to reduce the risk of or progression of cancer. The method comprises administering to a subject, who is known to be at risk for cancer or is diagnosed with cancer, an agent for inhibiting interaction of an activating ligand with a portion of a cell surface receptor that interacts with the activating.

Another method of the invention involves treating a subject to reduce the risk of or progression of cancer. The method comprises administering to a subject, who is known to be at risk of cancer or is diagnosed with cancer, an agent for preventing clustering of portions of cell surface receptors that interact with an activating ligand such as a growth factor.

Another method involves diagnosing a physiological state indicative of cancer or potential for cancer. The method comprises determining a specific cleavage site of MUC I distinguishable from a different cleavage state of MUC I.

Another method of the invention involves treating a subject having a cancer characterized by the aberrant expression of MUC 1 . comprising administering to the subject etomoxir in an amount effective to reduce tumor growth.

Another method of the invention involves treating a subject having a cancer characterized by the aberrant expression of MUC I, comprising administering to the subject L-cc-methyl-dopa in an amount effective to reduce tumor growth.

Another method of the invention for treating a subject having cancer characterized by the aberrant expression of MUC I, comprises administering to the subject calcimycin in an amount effective to reduce tumor

growth.

Another method for treating a subject having a cancer characterized by the aberrant expression of MUC 1, comprises administering to the subject butylindazole in an amount effective to reduce tumor growth.

. . .

imply a disease-related cleavage site on the MUCI receptor;

Fig. 4 is a graph of percent cell proliferation that shows that an antibody against an epitope of the MUC I receptor which is proximal to the cell surface, and that dimerizes the receptor, enhances cell proliferation in a manner typical of a growth factor/receptor - antibody interaction;

Fig. 5 is a graph of percent cell proliferation that shows that an antibody against an epitope of the MUC I receptor which is proximal to the cell surface, and that dimerizes the receptor, dramatically enhances. . . used to detect inhibitors of the MUC 1 -Ligand interaction;

Fig. 13 shows a histogram illustrating the selective inhibition of proliferation of tumor cells that aberrantly express the WC I receptor, in response to treatment with compounds of the invention, and lack of an effect. . . of the WC I receptor and a multimerizing ligand(s);

Fig. 15 shows a histogram illustrating the selective inhibition of proliferation of tumor cells that aberrantly express the WC I receptor, in response to treatment with drugs that specifically inhibit MUCl positive cells;

Fig. 16 shows. . . to treatment with drugs that non-specifically inhibit cell proliferation;

Fig. 17 shows a histogram illustrating that drugs that selectivly inhibit proliferation of tumor cells that aberrantly express the WC I receptor bind to the PSMGFR, while drugs that non-selectively inhibit cell proliferation do not;

Fig. 18 is a graph showing that the inhibition of WC 1 -dependent cell proliferation induced by an anti-tumor drug identified in accordance with the invention, is modulated when a synthetic peptide, corresponding to the portion of MUC I that. .

. . .

a mechanism in which this portion is made accessible to the ligand upon MUC I cleavage at a site associated with tumorigenesis that causes release of the IBR from the cell.

. . .

shed, or cleaved. The cleaved IBR of interest is a disease-associated cleavage, i.e. that type of cleavage that can result in cancer.

. . .

ratio with the IBR and forms part of the portion of MUC I that is shed upon cleavage in healthy and tumorigenesic cells.

. . .

type of interaction that occurs between pairs of molecules including proteins, nucleic acids, glycoproteins, carbohydrates, hormones and the like. Specific examples include

antibody/antigen,
antibody/hapten, enzyme/substrate, enzyme/inhibitor,
enzyme/cofactor, binding
protein/substrate, carrier protein/substrate, lectin/carbohydrate,
receptor/hormone,
receptor/effector, complementary strands of nucleic acid,
protein/nucleic acid
repressor/inducer, ligand/cell surface receptor, virus/ligand, etc.
. . .
the host system includes a synthetic species such as a polymer,
dendrimer,
etc., or a naturally-occurring species, for example an IgM
antibody, which is not simply
naturally present in the host system but is added to the host system
from a source
external to. . .
. . .
a dimer, a
tetramer, a higher multimer, or a complex comprising a plurality of
molecular species. In
the context of MUC I tumor cells, an activating ligand can be
a species produced by the
cells that interacts with the MGFRs on the surface of the WC 1
tumor cells in a manner
that effects inductive multimerization.

A MUC I presenting cell refers to both non-cancerous and
cancerous cells
expressing MUC I and/or MGFRs on the surface. A WC I tumor
cell or NWC 1
cancer cell or cancerous MUC1 cell refers to a
cancerous tumor cell that aberrantly
expresses MUC I and/or MGFR on its surface.
. . .
limited to, a
binding species such as a peptide synthesized on a polystyrene bead, a
binding species
specifically biologically coupled to an antibody which is
bound to a protein such as
protein A, which is attached to a bead, a binding species that forms.
.
. . .
cover in this coritext, means that there is no portion of the surface or
3o region that directly contacts a protein, antibody, or other
species that prevents complete,
direct coverage with the SAM. Le. in preferred embodiments the surface
or region
includes, across its. . .

The term cancer, as used herein, may include but is not
limited to: biliary tract
cancer; bladder cancer; brain cancer
including glioblastornas and medulloblastomas;
breast cancer; cervical cancer; choriocarcinoma;
colon cancer; endometrial cancer;
esophageal cancer; gastric cancer; hernatological
neoplasms including acute lymphocytic
and myelogenous leukemia; multiple myelorna; AIDS-associated leukemias
and adult T-
cell leukemia lymphoma; intraepithelial neoplasms including
Bowen's disease and
Paget's disease; liver cancer; lung cancer;
lymphomas including Hodgkin's disease and
lymphocytic lymphomas; neuroblastornas; oral cancer including
squarnous cell

carcinoma; ovarian cancer including those arising from epithelial cells, strornal. cells, germ cells and mesenchyrnal cells; pancreatic cancer; prostate cancer; rectal cancer; sarcomas including leiornyosarcorna, rhabdornyosarcoma, liposarcoma, fibrosarcoma, and osteosarcoma; skin cancer including melanoma, Kaposi's sarcoma, basocellular cancer, and squarnous cell cancer; testicular cancer including germinal tumors such as serninorna, non-serninorna (teratornas, choriocarcinomas), stromal tumors, and germ cell tumors; thyroid cancer including thyroid adenocarcinoma and medullar carcinoma; and renal cancer including adenocarcinorna and Wilms tumor . Preferred cancers are; breast, prostate, lung, ovarian, colorectal, and brain cancer .

The term cancer treatment as described herein, may include but is not limited to: chemotherapy, radiotherapy, adjuvant therapy, or any combination of the aforementioned methods.. . .

Another treatment for cancer is surgery, which can be utilized either alone or in combination with any of the aforementioned treatment methods. One of ordinary. . .

An agent for prevention of cancer or tumorigenesis means any agent that counteracts any process associated with cancer or turnorigenesis described herein. For example, an agent that interacts with (e.g, binds to) to MGFR thereby reducing or preventing interaction, with. . .

. . .
in a cell-free assay containing the enzyme and WC I receptors, and the the rate or position of cleavage measured by antibody probing, Polymerase Chain Reaction (PCR), or the like. Alternatively, without first identifying enzymes that affect WC 1, agents are screened against cells. . . present WC 1, the supernatant removed, and the cell remain tested for accessibility of the MGFR portion, e.g. using a labeled antibody to the MGFR. Agents can be identified from commercially available sources such as molecular libraries, or rationally designed based on known agents. . .

. . .
reduces cleavage of the WC I receptor at any location. Such an agent can be used to treat a subject having cancer or at risk for developing cancer because if cleavage is prevented, then the accessibility of the MGFR, a functional receptor associated with cancer, is reduced or prevented. Such agents can be selected by exposing cells to a candidate agent and determine, in the supernatant,. . .

. . .
A subject, as used herein, refers to any mammal (preferably, a human), and preferably a mammal that may be susceptible to tumorigenesis or cancer associated with the abherrant expression of MUC I. Examples include a human, non-human

primate,
cow, horse, pig, sheep, goat, dog, or cat.. . .

The present invention involves, generally, novel molecular targets for drug
screening, therapeutics and diagnostics related to cancers
that are characterized by the
aberrant expression of a class of cell surface receptors characterized by interchain
binding regions. One such set of cancers are those
characterized by the aberrant
3 o expression of MUC I. Much of the description of the invention herein
involves. . . to identify other cell surface receptors that
function by this or a similar mechanism, and to apply the invention to those cancers
characterized by aberrant expression of receptors. The invention is based on a novel
mechanism involving cell surface receptors that have regions that. . .
. .
and progressing away from the cell. In
at least one U.S. provisional patent application (earlier
application(s)) filed by the
same inventors, entitled Tumor Markers and Drug Screening for Tumorogenesis
Inhibition, relating to MUC I diagnostics and other techniques, at least one region of
MUC I was defined differently. It is to. . .

Cleavage of MUC1 may occur at a site at or near the C-terminal boundary of the
IBR in tumor or cancer cells (between the cell and
the IBR), releasing the IBR from the
cell. Altematively,cleavageofWC1mayoccurwithintheIBRitselftocause
sufficient disrupting of the IBRs such that the. . .
. .
from intreacting with the MGFR portion of the
receptor, which is proximal to the cell relative to the IBR. In a cancerous or tumor cell,
this reticulum may be lost, allowing ligand interaction with the MGFR.
. .
proliferation; and (b) blocking the interaction
of this portion of the WC I receptor (MGFR) with its ligand(s), blocks cell
proliferation. When tumor cell lines, in which the WC I
receptor is homogeneously
expressed across the entire cell surface, are treated with an IgG antibody raised against
the MGFR portion of the WC I receptor, the rate of cell proliferation is greatly
enhanced, see Fig. 5. Since IgG antibodies are bivalent, i.e.
one antibody simultaneously
binds to two adjacent MGFR portions on the cell surface, these results demonstrate that
the antibody acts as an activating ligand, mimicing the effect
of a growth factor, which
dimerizes MGFR portions, and thus triggers a cell. . . of the receptor with a
monomeric composition, thus preventing inductive multimerization and subsequent
signaling cascades. For example, a single chain, or monovalent, antibody raised against
the MGFR portion of the MUC1 receptor would function as an effective anti-cancer
therapeutic. Another therapeutic strategy is to block the activity of enzymes that modify

the receptor, which may be required for some ligand. . .

. . .
histidine tag of the peptide, the beads were then incubated with lysates and supernatants from a variety of cell types, including cancer cell lines that overexpress MUCL Enzyme inhibitors such as PMSF were added to some of the lysates and supernatants to circumvent problems. . .

. . .
containing some or all of these ligand species. In one aspect, the invention involves modification and use of the above species as anti-cancer agents.

. . .
a protein known as Metastasis Inhibition Factor NM23, which has been implicated in both the promotion and inhibition of metastasis of human cancers. Whether the role of NM23 is a tumor supressor or promoter may depend on the type of cancer. In ovarian, colon and neuroblastoma tumors, NM23 overexpression has been linked to a more malignant phenotype (Schneider J, Romero H, Ruiz R, Centeno MM, Rodriguez-Escudero FJ, NM23 expression in advanced and borderline ovarian carcinoma, Anticancer Res, 1996; 16(3A): II 97-202). However, breast cancer studies indicate that reduced expression of NM23 correlates with poor prognosis (Mao H, Liu H, Fu X, Fang Z, Abrams J, Worsham MJ, Loss of NM23 expression predicts distal metastases and poorer survival for breast cancer, Int J Oncol 2001 Mar; 1 8(3):587-91).

. . .
NOT added to lysate) corresponded to more than one protein species, including 14 3, which is a signaling protein implicated in many cancers, and cathepsin D, which is a protease and is also implicated in tumor progression. 14 3 exists as a dirner and can simultaneously bind to two, identical phospho-serine peptides. This protein has been shown to. . .

. . .
a high degree of homology to beta-lipotropin (Odell W, Wolfsen A, Bachelot 1, and Hirose F, (1979) Ectopic production of lipotropin by cancer The American Journal ofMedicine 66; pgs.

. . .
the position of enzyme cleavage is associated with receptor clustering, accessibility of adjacent portions of the receptor to putative ligands, and thus cancer. Agents that modulate the activity of this enzyme may be potent anti-cancer agents. Additionally, an early diagnostic test for cancers that aberrantly express MUC 1 may be based on detecting the portion of MUC I that self-aggregates (113R) circulating in bodily. . . cell surface after the release of the portion that self-aggregates (IBR - some or all of the PSIBR sequence) may be potent anti-cancer drugs. In addition, agents that block binding

of the natural ligand to the remaining portion after the release of the IBR,. . . biomolecules and to artificially cluster the MGFRs. Another alternative agent, which can be used to artificially cluster the MGFRs is an IgM antibody raised against the MGFR or PSMGFR. This artifically-induced clustering may serve to keep the cytoplasmic tails clustered to prevent interaction with intracellular. . .

One aspect of the invention involves s novel drug screening assays, that identify therapeutics that interfere with the proliferation of tumor cells that aberrantly express MUC L The drug screen makes use of the new molecular target for cancer that is disclosed herein. Another aspect of the invention involves therapeutics identified by the drug screen. Yet another aspect of the invention involves methods for diagnosing MUC I+ cancers, which is based upon the mechanism elucidated by the inventors.

. assay which can rapidly identify agents that interrupt the interaction between the MGFR and its ligand(s) and thus can be used as cancer therapeutics, (see Example 5a and Fig. 12 for details).

60/317,302 and 60/317,314, both filed on September 5, 2001 and entitled COMPOSITIONS AND METHODS OF TREATMENT OF CANCER.

Agents so identified may be potent anti-cancer agents either in monomeric form or as polymers or dendrimers. Drug libraries and peptide libraries can be screened for molecules that inhibit. . .

. its ligands. These methods include but are not limited to phage display methods, yeast two-hybrid system, sandwich assays, surface plasmon resonance-based assays, antibody-based assays, peptide bead assays for testing with drug libraries, bead assays, GFP-reporter assays, and the like. Ligands to the MGFR portion. . .

. used to block binding of the remaining extracellular portion of cleaved MUC I to its natural ligand, and can potentially inhibit cancer growth.

. of the invention is a drug screening assay for identification of drugs that can be useful for prevention and/or treatment of cancer by altering the cleavage state of WC 1 receptors on cells. In such assays, described in more detail below, cultured cells are. . . and/or dosage or other conditions involving exposure to the drugs. These cells can be derived from a particular patient, or can be tumor-associated or non-tumor-associated cell lines. Customized therapeutic protocols can be determined for a particular patient in this manner. The invention involves, in one aspect, treating. . . below, shown to affect the cleavage state of WC I of the patient's cells in a manner that

prevents, inhibits, or reverses cancer.

. . .

suspected that the incorrect cleavage of WC 1 on the surface of the cell causes the cascade leading to proliferation and tumorigenesis, it would be advantageous to test candidate drugs in a whole cell assay for their ability to affect enzyme cleavage or the. . .

Colloids bearing an antibody, natural ligand, or small molecule that binds to either the cleaved portion of WC I, or the remaining extracellular portion (plus. . .

. . .

contained within the shed fragment. The aggregation potential of peptides released into the cell media is tested by adding colloids bearing an antibody to a sequence distal from the self-aggregating portion, but not a repeat sequence. In this way, antibody-presenting colloids would attach to upstream regions of MUCL If the self-aggregating region was also attached to the released fragment, then this would. . .

. . .

of these portions or other structural constraint that inhibits their association with factors that promote cell proliferation. Alternatively, IgM-type monoclonal or polyclonal antibodies raised against the MGFR or PSMGFR could be utilizied. Each anti-MGFR IgM antibody could be able to aggregate ten MGFRs on the cell surface to form preventative clusters.

. . .

I receptor can similarly be modified with other therapeutic agents. In this way, such a therapeutic can be directed to the tumor cells. For example, an agent that binds to the MGFR region of the WC 1 receptor can be modified with a radioactive substance to destroy tumor cells that aberrantly express the WC I receptor. Other toxic substances, such as ricin, as well as other therapeutics, can be. . . that bind to the MGFR could be modified to present a imaging agent for use in diagnostic imaging of MUC 1+ tumors and metastases. Such ligands can also, alternatively, be modified to act as drugs that can be useful for prevention and/or treatment of cancer. In one embodiment, a ligand, which in its unmodified form binds to multiple MGFRs causing inductive multimerization, is modified to remove or. . .

The discoveries presented herein: (1) that the IBR of MUC I self-aggregates; (2) that an antibody that dimerizes adjacent MGFR portions of the MUC I receptor leads to proliferation of WC I presenting tumor cells; and (3) that proliferation of MUC I presenting tumor cells can be inhibited by treatment with agents that target the MGFR and block the MGFR against interaction with a ligand,. . . the cell that WC I remains clustered, and the MGFR is inaccessible to ligands

such
as growth factors, and in a tumor cell, MUC I cleavage occurs
such that enough of the
IBR is cleaved from the cell such that WC I does. . .

The above-mentioned mechanistic model predicts that in a subject with a
WC I -
dependent tumor or who is prone to developing such a
tumor, the portion of the MUC I
receptor that is shed will contain the IBR region of the receptor,
leaving the MGFR
portion. . .

The cleavage state will differ between a healthy cell and a cell with
tumor potential. The
cleavage state determination can involve determining whether cleavage
occurs in a
manner such that the normal interaction between the IBRs. . .
. . .
and/or a signaling entity. Generally, an assay as
described in WO 00/43791 or WO 00/34783 can be used. In a specific
example,
antibodies to a portion of MUC I that would remain fastened to
the IBR if the IBR is
cleaved from the cell, such as antibodies to the repeats
domain, are fastened to colloids.

The discovery that tumor cells can be treated with an agent
that binds to the
MGFR of MUC 1, or a ligand of MGFR, in a manner that inhibits cell
proliferation leads
to the conclusion that, in a diseased cell (a cancerous cell
or a cell with potential for
becoming cancerous), cleavage of MUC I occurs in a manner that
allows MGFR to
interact with at least one ligand in a manner that promotes
turnorigenesis or cancer.
. . .
separated from the cell. The amounts of various receptor regions
may be determined with any type of binding assay, e.g. an
antibody-binding assay. For
example, antibodies that specifically bind to the constant
region or the repeats may be
attached to surfaces (e.g. magnetic beads) to preconcentrate shed MUC I
receptors prior
to determining levels of IBR present. Then, for example, after
pre-concentration of
circulating MUC I receptors, antibodies to the IBR and
antibodies to the constant region
can be allowed to bind to the cleaved receptors, and determination of
the ratio of binding
of these antibodies reveals the ratio of IBR present relative
to constant region present in
the cleaved receptors, which in turn reveals the amount. . . IBR
relative to constant region present) for
detecting IBR at a cell surface is an indicator of the presence of a
tumor or the potential
for the development of a tumor. A ratio that approaches 1: I
when detecting these
regions in shed receptors is likewise an indicator of cancer
potential. This determination
can indicate potential for tumor formation, existence of a
tumor, progression of
tumorigenesis, etc., and can thereby serve as a diagnostic
and/or a evaluator of treatment

for tuniorigenesis
Another diagnostic aspect of the invention involves. . . assay or a colloid bead assay (See above
discussion and Examples, below). Alternative techniques involve determining the
presence of the IBR using antibody probing assays,
hybridization, PCR Reverse
Transcriptase PCR (rtPCR), Ligase Chain Reaction (LCR), cycling probe technology,
etc. In a preferred embodiment of the. . .

The determination, in a blood sample, of the amount of cleaved receptor carrying
IBR, either involving antibody binding ratios, colloid binding assays, or the like can be
made on a bodily fluid sample, such as a blood sample and optionally compared with
other samples (e.g. to monitor the subject's progression of tumorigenesis or progression
for treatment of the same) and/or controls.

. .
site can be studied without removal of the tissue
from the subject). In either of these studies, a primary indicator of tumorigenesis or
potential for tumorigenesis is the amount of MGFR at a cell surface accessible to
interaction with external agents such as growth factors, etc. This determination can be
made, for example, by determining the amount of an antibody to the MGFR region that
binds to the sample, either using standard antibody binding study techniques, or by
exposing the sample to colloids to which antibodies specific to the MGFR region have
3o been immobilized and determining binding of the colloids to the samples using
techniques described in International patent publication numbers WO 00/34783 and WO
00/43791, referenced above. In another technique (perhaps more suited for an excised
sample), antibodies to the MGFR region and to the IBR can be exposed to the sample
and a determination made of the ratio of binding of each to the sample. A healthy
sample will exhibit little or no antibody binding to the MGFR region. A sample
indicating turnerigenesis or potential for tumorigenesis will show a non-zero ratio of
MGFR antibody binding to IBR antibody binding.

. .
a cell surface (rather than the amount of IBR in a shed portion) in a sample from a subject to evaluate cancer, or the potential to develop cancer in a subject.

. .
information as to whether the IBR
remains on the cell surface, or was shed from the cell surface, giving indication of cancer
or turnorigenesis or the potential for either, as discussed above. Determining the site of
cleavage can be accomplished by using enzyme-amplification methods. .

. .
pre- and post-treatment levels of
cleaved cell surface receptor IBR, or cell surface receptor IBR at the surface of a cell, in

cancer cells or tissues may be used to diagnose cancer in a subject or assess the effectiveness of treatment in a cancer patient. In a preferred embodiment the cell surface receptor is MUC 1.

Comparison of the levels of the above-mentioned regions with levels from subjects known to be free of cancer may allow determination of the presence of cancer in the subject. An example, although not intended to be limiting, is that a determination of the presence of elevated levels of. . . in a sample from a subject, when compared to a level determined in samples from control subjects, may suggest the presence of cancer in the subject with elevated levels. Such methods of comparing levels of cancer-associated markers between a sample from a subject and a control sample for diagnostic purposes would be understood by one of ordinary. . .

Examples of such methods include Western blotting, ELISA, antibody precipitation, PCR, LCR, rtPCR, cycling probe technology, and colloidal assays as described in international patent application serial no. PCT/USOO/01997, filed 01/25/00, entitled 5Rapid. . .

. . .

aspect of the invention, the cleavage state of MUC I can be used to determine progression or regression of a subject's cancer over time. The cleavage state also can be used to assess treatment parameters including, but not limited to: dosage, method of administration,. . .

1 5 Another aspect of the invention involves extremely early-stage cancer diagnosis.

This aspect involves identification of patients who may be at risk for developing tumor or cancer associated with abnormal cleaveage of MUC L These patients may not have developed tumors, but may exhibit a cleavage state indicative of a condition that can lead to cancer. In some instances, the subjects will already be undergoing treatment for 20 cancer, while in other instances the subjects will be without present cancer treatment. A test for a genetic predisposition to cancers characterized by aberrant MUC 1 expression of the invention is based on detecting genetic alterations in the MUC I cleavage enzyme(s), over. . .

The fact that elevated levels of cleaved MUCl are found in the blood of cancer patients is the basis for a blood test for breast cancer, which is not described herein.

. . .

is the identification of compounds that directly bind to the PSMGFR portion of the receptor. Therefore, a sensitive method for diagnosing early tumors is to administer to the patient, compounds that bind to the PSMGFR region that have also been derivatized with contrast or imaging agents. These

compounds will
agglomerate onto tumors wherein this portion of the NWC I
receptor is accessible.

. . .

one aspect of the invention is directed to methods for
treating a subject diagnosed with or at risk of developing a
cancer or tumor characterized
by the aberrant expression of MUCL The treatments of the present
invention involve the
use of drugs or agents as described herein. That is, one aspect involves
a series of
compositions useful for treatment of cancer or tumor
characterized by the aberrant
expression of MUC I, including these compositions packaged in kits
including
instructions for use of the composition for. . . a description of use
of the composition for participation in any biological
or chemical mechanism disclosed herein that is associated with
cancer or tumor. The kit
also can include instructions for use of a combination of two or more
compositions of
some embodiments of the invention.. . . via another known route of
drug delivery. These and
other embodiments of the invention can also involve promotion of the
treatment of
cancer or tumor according to any of the techniques
and compositions and combinations
of compositions described herein.

. . .

even though the patients exhibit indication for treatment of one of the
compositions of the invention for a condition different from
cancer or tumor, including
conditions that can be unrelated to cell proliferation or conditions
that can accompany
cell proliferation, cancer, or tumor. That is, if a
composition of the invention is known
for treatment of a different condition, some embodiments of the present
invention also
involve use of that composition for treatments that accompany cell
proliferation, cancer,
or tumor disease where indicated. These and other embodiments
of the invention can
include such treatment where the dosage, delivery technique or vehicle,.
. . timing of administration, or other
factor differs from the use of the composition for treatment of the
condition different
from cell proliferation, cancer, or tumor. In
another set of embodiments, treatment of
.cell proliferation, cancer, or tumor with
compositions of the invention may occur under
5 conditions that are similar to or overlap the use of compositions of.
. . the invention for
treatment of a different condition, but the compositions of the
invention are promoted for
treatments that accompany cell proliferation, cancer, or
tumor or includes instructions for
treatments that accompany cell proliferation, cancer, or
tumor as mentioned above. As
used herein, promoted includes all methods of doing business including
methods of
education, hospital and other clinical instruction,. . . written,
oral, and electronic communication of any form, associated with
compositions of the invention in connection with treatments that
accompany cell
proliferation, cancer, or tumor. Instructions can

and often do define a component of promotion, and typically involve written instructions on or associated with packaging of compositions. . .

Subjects for whom certain treatment methods of the invention (with specific compositions directed toward cell proliferation, cancer, or tumor) are not intended are those who are diagnosed with a condition which may already call for treatment with the specific composition. Accordingly, one aspect of the invention involves treatment of cell proliferation, cancer, or tumor with a specific composition disclosed herein for that purpose, not in combination with another agent where the other agent has been taught previously for use in treatment of cell proliferation, cancer, or tumor itself. Another embodiment involves treatment of cell proliferation, cancer, or tumor with this specific composition alone, not in combination with any other active agent. Another embodiment involves treatment of cell proliferation, cancer, or tumor with this specific composition where the use of the composition in the treatment is specifically instructed (through, e.g.

written instructions that can accompany the composition) for the treatment of cell proliferation, cancer, or tumor. In a preferred embodiment of this aspect, the invention involves treatment of cell proliferation, cancer, or tumor with the specific composition where the use of the composition in the treatment is specifically instructed to affect a mechanism associated with cell proliferation, cancer, or tumor as disclosed herein.

.
treated with dru s useful according to
I 9
certain methods of the invention, including patients who are not suffering from cell proliferation, cancer, or tumor and who may or may not be presently indicating susceptibility to cell proliferation, cancer, or tumor . In other words, the preventative treatment preferably is directed to patient populations that otherwise are free of disease symptoms that call for. . .

.
NS 1 619 and etomoxir interrupt the interaction of MGFR with its ligand(s) that otherwise would bind to MGFR and promote tumorigensis.

In this aspect, the invention involves treatment of subjects associated with tumor or
cancer associated with aberrant expression of MUC1 with these agents or a combination.

.
interfering with the MGFR-ligand interaction. All of the compounds inhibited cell proliferation, but roughly half of the compounds were toxic to both tumor cells that presented the MUC I receptor as well as

cells that did not present this receptor. As discussed herein, the. .
.
. . .
to the MGFR
1 5 portion will have little or no toxic effects. Fusaric acid,
L-U.-methyl-dopa and etomoxir
selectively inhibited proliferation of tumor cel Is presenting
MUC I while leaving control
cells unaffected, see Fig. 13.
. . .
treatment with fusaric acid, but where the call for treatment with
fasaric
acid did not specifically call for treatment directed toward
tumors or cancers associated
with the abherrant expression of WC I, particularly in the dosages or
other specific
protocols described previously in U.S. Patent No. 6,127,393. Specific
diseases listed in
U.S. Patent No. 6,127,393 include skin cancer, breast
cancer, prostate cancer, cervical
cancer, colon cancer, liver cancer and
lung cancer. In one embodiment, the methods of
the present invention involve treatment with fusaric acid in dosages
lower than that
described in U.S.. . .
. . .
to
the subject any one of calcimycin, fusaric acid, L-cc-methyl-dopa,
butylindazone,
NS 1619 and etomoxir in an amount effective to lower the
risk/prevent/reduce/inhibit
tumors or cancer associated with aberrant expression
of MUC 1.
. . .
the specific route
of administration and like factors within the knowledge and expertise of
the health
practitioner. For example, in connection with tumor or
cancer associated with ablierrant
expression of NWC1, an effective amount is that amount which prevents
interaction of
MGFR with its ligand that otherwise. . .
. . .
(for agents that act according to that
mechanism) so as to slow or halt the development of or the progression
of tumor or
cancer associated with aberrant expression of MUC 1. It is
preferred generally that a
maximum dose be used, that is, the highest. . .
. . .
administer higher
and more frequent doses of the agent to a subject for example during or
immediately
following a event associated with tumor or cancer,
provided still that such doses achieve
the medically desirable result. On the other hand, it may be desirable
to administer lower
2o. . .

As noted, different drugs act according to different mechanisms. Drugs
according to one mechanism interfere with MGFR binding to a
tumorigenesis-promoting
ligand, and do so to a particular degree relative to natural conditions
for the subject in the
io absence of the drug.. . .

routes are available. The particular mode selected will depend, of course, upon the particular combination of drugs selected, the severity of the cancer condition being treated, the condition of the patient, and the dosage required for therapeutic efficacy. The methods of this invention, generally.

Parenteral routes include subcutaneous, intravenous, intramuscular, or infusion. Direct injection may be preferred for local delivery to the site of the cancer. Oral administration may be preferred for prophylactic treatment e.g., in a subject at risk of developing a cancer, because of the convenience to the patient as well as the dosing schedule.

(e.g. tissue), such as (e.g. the vascular cell wall), by coupling the liposome to a specific ligand such as a monoclonal antibody, sugar, glycolipid, or protein.

Use of a long-term sustained release implant may be particularly suitable for treatment of established cancer conditions as well as subjects at risk of developing a cancer. Long-term release, as used herein, means that the implant is constructed and arranged to deliver therapeutic levels of the active ingredient for at least 7 days, and preferably 30-60 days. The implant may be positioned at the site of the tumor.

The therapeutic agent may be administered in alone or in combination with an anti-cancer drug. If the therapeutic agent is administered in combination the compounds may be administered by the same method, e.g. intravenous, oral, etc. or may be administered separately by different modes, e.g. therapeutic agent administered orally, anti-cancer drug administered intravenously, etc. In one embodiment of the invention the therapeutic agent and the anti-cancer drug are co-administered intravenously. In another embodiment the therapeutic agent and the anti-cancer drug are administered separately.

Anti-cancer drugs that can be co-administered with the compounds of the invention include, but are not limited to Acivicin; Aclarubicin; Acodazole Hydrochloride; Acronine;.

HHHHHHGFLGLSNIKFRPGSVVVQLTLAFRE (SEQ ID NO: 4)
Histidine-Tagged Repeat Motif 2 (His-RM2).

GFLGLSNIKFRPGSVVVQLTLAFRE (SEQ ID NO: 8)
Repeat Motif 2 (RM2).

Histidine-tagged peptides were synthesized with the sequences shown in table 1 (the various regions of MUC 1). The lyophilized peptides were. 2.

Row A contains the
His-PSIBR (primary sequence interchain binding region) peptide; Row B contains the
His-TR peptide; Row C contains the His-RM2 peptide; Row D contains the His-
PSMGFR peptide. Column 1 contains the His-PSIBR peptide; Column 2 contains the
His-TR peptide; Column 3 contains the His-RM2 peptide; and Colurrm 4 contains the
His-PSMGFR peptide. The solutions were observed for a color change. A change in
solution color from. . . sequence of the
interchain binding region (PSIBR), self-aggregates in a high affinity interaction,
suggesting a mechanism by which the MUCl receptor confers tumorigenesis.

Example lb: Relationship Between MUCI Cleavage Site in Tumor Conditions
and NWC I Interchain Bindi
This example investigates the ability of peptide sequences near the boundary
between the MGFR and P SIBR. . . the MUC 1 receptor to participate in self-aggregation,
and thereby elucidates a probable cleavage site of NWC I that is associated with
tumorigenesis or cancer.

This strongly suggests that cleavage of the MUC I receptor in tumors or cancers
associated with aberrant expression of MUC I occurs at or near the boundary between the
PSMGFR and PSIBR sequences, since it is demonstrated herein that in tumor cells that
overexpress MUC I, the MGFR is accessible by agents that reduce cell proliferation by
inhibiting the interaction between MGFR and. . . otherwise would promote cell proliferation. This also strongly suggests that the IBR is shed in cleavage of MUC I receptor in tumor or
cancer associated with aberrant
expression of WC I, but is not shed in cleavage of MUC I when WC I is normally
expressed. . . That is, that the cleavage site of MUC I is at or near the C-
terminal boundary of the IBR in tumor or cancer
cells and IBR at or near the N-terminal
boundary of the IBR in healthy cells.

In the remaining examples, the mechanism described above for cancer associated
with aberrant expression of MUC I, in which an activating ligand (which is a growth
factor) binds to multiple MGFRs at. . . which causes proliferation (inductive multimerization), is confirmed. Briefly, the
mechanism is confirmed by showing that exposure of cells to a bivalent antibody raised
2o against MGFR induces cell proliferation characterized by a growth/response curve
typical of a growth factor/receptor - antibody response (Example 2, below); the
activating ligand produced by MUC I -presenting cells binds multiple PSMGFRs, and the
amount of activating ligand. . . each cell type is proportional to the amount of
MUC I receptor produced by that cell type (Example 3a-b, below); MUC1

tumor cells
produce a species that is a multimer (Example 4b, below); and drugs found to be specific
for MUC I tumor cells (drugs that inhibit proliferation in MUC 1 tumor cells but not other
cells) are shown to bind to MGFR at cells, while those that are not specific (those that
inhibit MUC I tumor cells and other cells) are toxic in that they bind to the multimeric
ligand and thereby remove it from interaction with. . .
.
of the MGFR portion of the WC I receptor triggers enhanced
Cell Proliferation Consistent with the Mechanism Presented for MUC I Tumor Cells
This example demonstrates the effect of dimerization on the MUC I receptor. In
this example it is shown that exposure of cells to a bivalent antibody grown against the
MGFR region of the MUC I receptor, at varying concentration, results in enhanced cell
proliferation (or lack thereof) consistent with the mechanism presented for MUC1 tumor
cells. A bivalent antibody was raised against PSMGFR (i.e., a single antibody having
the ability to bind simultaneously to two MGFRs was produced). MUC I tumor cells
(T47Ds) were exposed to this antibody, and cell proliferation was studied as a ftinction
of concentration of the antibody. A growth/response curve typical of a growth
factor/receptor - antibody response was observed. Specifically, at concentration low
enough that only a small portion of the cells were exposed to the antibody, cell -
proliferation was low. At a concentration of antibody high enough that one antibody
could bind adjacent MGFRs, cell proliferation was maximized. At a high excess of
antibody, each antibody bound only a single MGFR, rather than dimerizing adjacent
MGFRs, and proliferation was reduced.

T47D (HTB- 1 3 3) cells, a human breast cancer cell line that overexpresses
MUC I, were cultured to 30% confluency. An antibody raised against the PSMGFR
portion of the WC I receptor, i.e. an antibody to the MFGR (Zymed, San Francisco,
California, USA), was added to cells at varying concentrations in a multi-well cell
culture plate. As a negative control, a second set of T47D cells was treated with an
irrelevant antibody (anti-streptavidin). Prior to adding antibody, cells were counted (at
time zero). All experiments were performed in triplicate. Cells were allowed to grow in
a C02 incubator under. . . well) at 24 hours and again at 48 hours. Results, see Fig. 4, show that in a
concentration-dependent manner, addition of antibody caused enhanced cell proliferation
compared to the proliferation of the same cells treated with a control antibody. Figure 4
is a graph in which measured cell growth at 24 and 48 hours is plotted as a function of
anti-PSMGFR concentration. At the optimal antibody

concentration, when presumably
one antibody binds bivalently to two MGFR portions of the WC I
receptor, i.e.

In a similar experiment, a concentration of the anti-PSMGFR
antibody,
identified to maximize cell proliferation, was added to a first group of
T47D tumor cells,
grown as described above. The same amount of the anti-PSMGFR
antibody was added
to a set of control cells, K293 cells. Figure 5 shows that the addition
of the anti-
PSMGFR antibody to MUC I tumor cells (T47D) enhanced
proliferation by 180% 24
hours, but had no effect on the control cells. The growth of the T47D
cells plateaued to
saturation, for cells with added antibody, at 48 hours.
Control cells never reached
saturation within the time frame of the experiment and were at 70%
confluency at. . .
.
Activating Ligand Produced by MUCI-Presenting Cells Binds
Multiple PSMGFRs
In this example, it is demonstrated that the activating ligand that
triggers MUC I
tumor cell proliferation binds multiple PSMGFRs
simultaneously. Colloid particles were
produced that carry immobilized PSMGFRs, and suspensions of these
colloids were
exposed to lysate and supernatants of (1) MUC1 tumor cells, or
(2) control cells. MUC I
tumor cell lysates/supematants caused the colloids to
aggregate (suspension turns blue)
because the activating ligand contained in them binds MGFRs on
different. . .

Lysates and supernatants from four different tumor-associated
cell lines (HTB- 1 3 3 (also
called T47D), CRL- 1 500, CRL 1504 and CRL- 1 902; ATTC, American Type.
. .
.
Rows E-H contained colloid particles carrying a random sequence
peptide. Columns 2, 5, 8, and I I contained lysates from a tumor
cell line that
overexpresses NWC1 (HTB-133). Columns 3, 6, 9, and 12 contained lysates
from a
tumor cell line that does not expresses WC 1 (CRL- 1 902).
Columns 1, 4, 7, and 1 0
contain lysates from a tumor cell line that expresses, but
does not overexpress, NWC I
(CRL- 1 504). Columns 1-3: NTA concentration on colloid: 20
microniolar;. . .
.
absence (Fig. IO) of the protease inhibitor PMSF
io (phenyl methyl sulfonyl fluoride). Lysates from T47D cells were used
because this
breast tumor cell line was known to overexpress MUC I;
additionally, the inventors
presented evidence herein (see Fig. 8A-D) that this cell line. . .
.
Culture Collection,
Manasses, VA) and are all breast carcinoma cell lines. Some lines have
been shown to
express or over express the tumor marker receptor MUC 1,
Her2/neu or the oncogenic

enzyme cathepsin K.

. . .

from Mediatech supplemented with I mM sodium
pyruvate, IO% FB S
Example 4b: Demonstration that the Ligand That Interacts with MUC 1
Cancer Cells
is a Multimer
In this example, it is demonstrated that a ligand produced by MUCl
cancer cells
that triggers cell proliferation in these cells is a multimer.

. . .

known as Metastasis Inhibition Factor NM23,
which has been implicated in both the promotion and inhibition of
metastasis of human
1 5 cancers. Whether the role of NM23 is a tumor
supressor or promoter may depend on the
type of cancer. In ovarian, colon and neuroblastorna
tumors, NM23 overexpression has
been linked to a more malignant phenotype (Schneider J, Romero H, Ruiz
R, Centeno
MM, Rodriguez-Escudero FJ, NM23 expression in advanced and borderline
ovarian
carcinoma, Anticancer Res, 1996; 16(3A): II 97-202). However, breast
cancer studies
indicate that reduced expression of NM23 correlates with poor prognosis
(Mao H, Liu H,
Fu X, Fang Z, Abrams J, Worsham MJ, Loss of mn23 expression predicts
distal
metastases and poorer survival for breast cancer, Int J Oncol
2001 Mar; 1 8(3):5 87-9 1).

. . .

from the protein gel band described in Figures
9 and IO and that are derived from a protein implicated in many
cancers called
Metastasis Inhibition Factor NM23 are shown below in Table 4. NM23
exists as a
hexamer and may recognize an unmodified form. . .

. . .

NOT
added to lysate) corresponded to more than one protein species,
including 14 3, which
is a signaling protein implicated in many cancers, and
cathepsin D, which is a protease
and is also implicated in tumor progression. 14 3 exists as a
dimer and can
simultaneously bind to two, identical phospho-serine peptides. This
would dimerize the
MGFR portion. . .

. . .

QPGITFIAAK
3) human annexin V with Proline substitution by Thrionine gi: 3212603
GLGTDEESILTLLTSR
DLLDDLKSELTGK
SEIDLFNIR
Examples 5a-d: Drug Studies Consistent with Mechanism Presented for MUC1
Cancer
In these examples, drugs that inhibit proliferation in MUC I
tumor cells
specifically were compared to drugs that inhibit proliferation in both
MUC1 tumor cells
2o and other cells. Drugs, both specific and non-specific, were
identified by exposing them
to PSMGFR-presenting colloids in the presence of WC 1 tumor
cell lysates. Drugs
were identified as those that prevented colloid-colloid interactions.

Cell studies resulted
in a separation of these drugs into two groups - a group specific for MUC I tumor cells
and a non-specific group. Non-specific drugs did not bind to PSMGFR, but are
presumed to bind the activating ligand, and inhibit. . . somewhat toxic to both
cell types, since they remove the activating ligand from interaction with the cells. Drugs
specific for WC 1 tumor cells were found to bind to PSMGFR on beads, as
demonstrated by HPLC analysis of the product of cleavage of PSMGFR. .
.
. . .
of the MUC I Recepto
with its Activating Ligand(s)
The following is an example of a working drug screening assay to identify anti-
cancer agents. In this example, a histidine-tagged peptide
derived from the portion of the
MUC I receptor that remains attached to the. . .

The data below demonstrates the ability of anti-tumor drugs identified in
accordance with the invention, specifically, calcimycin, fusaric acid, L-(X-methyl-dopa,
butylindazone, NS 1 619 and etomoxir to inhibit proliferation of. . .
. . .
the interaction of the MGFR portion of the receptor with its activating ligands will
block the proliferation of MUC I -presenting tumor cells. Therefore, drugs that were
I 0 identified using the in vitro drug screening assay described in Example 5a were tested. . .
. . .
compared. As seen in Fig. 13, Etomoxir, L-alpha-
methyl DOPA, and Fusaric acid selectively inhibited proliferation of the NWC I -
expressing tumor cells over K293 negative control cells. The DMSO control cells (both
T47D and K293) show that DMSO alone does not effect cell proliferation. Fig. 13 is a
histogram illustrating the selective inhibition of proliferation of tumor cells that
aberrantly express the MUC I receptor (T47D cell line), in response to treatment with
compounds of the invention, and lack. . .
. . .
that were shown in the ftinctional cell
proliferation assay (see Example 5b) to selectively inhibit the proliferation of WC I -
presenting tumor cells by either directly binding to the MGFR portion or by acting on its
modifying enzymes. Figure 15 is a bar graph that compares the percentage cell growth
of WC 1 tumor cells (T47Ds) to a control cell line (K293 s), in response to treatment
with novel drugs, (described in greater detail in. . .
. . .
provisional patent applications serial nos. 60/317,302 and 60/317,314, both filed on
September 5, 2001 and entitled COMPOSITIONS AND METHODS OF TREATMENT
OF CANCER). As is readily apparent, this group of drugs dramatically inhibited or
completely prevented the proliferation of WC I -presenting tumor

cells, while leaving
the control cells, in most cases, unaffected.

. . .

provisional patent
applications serial nos. 60/317,302 and 60/317,314, both filed on
September 5, 2001 and
entitled COMPOSITIONS AND METHODS OF TREATMENT OF CANCER) on
cell
growth for WC I -presenting cells (T47D) and a control cell line (K293).
Notably, this
group of drugs, which presumably. . .

. . .

6: Modulation of Inhibitory Effect of Etomoxir on Cell Proliferation
Etomoxir, identified as a composition useful in treatment of NWC 1
-dependant
tumors in this invention, was shown to be specific for MGFR by
modulating its effect on
cell proliferation via competetive inhibition of. . .

. . .

Drugs That Affect MUC 1 Cleavage State
The release of the MUC I IBR can be correlated to the progression of
cancer.

Tumor derived cells expressing a cell surface receptor of the
type described
above, are cultured and treated with a drug candidate. Following. . .

Colloids bearing a binding peptide e.g. an antibody against a
constant region of the
receptor, remote from the enzyme cleavage site (amino acid 42 5 -479 for
MUC 1;
3o. . .

. . .

to the diagnostics and screening assays of the invention, the invention
relates to therapeutic methods for the treatment and prevention of
cancer and related
products. For instance, in one aspect the invention relates to a method
for treating a
subject having a cancer or at risk of developing
cancer by administering to the subject an
agent that reduces cleavage of a cell surface receptor IBR from a cell
surface receptor.

CLMEN 10 A method of treating a subject to reduce the risk of or progression
of cancer
comprising:
administering to a subject who is known to be at risk for cancer
or is diagnosed
with cancer an agent for inhibiting interaction of an
activating ligand with a portion of a
cell surface receptor that interacts with the. . .

16 The method of claim IO, wherein the cancers is selected
from the group
consisting of. breast, prostate, lung ovarian, colorectal, and
brain cancer.

31 A method of treating a subject to reduce the risk or of progression
of cancer
comprising:
administering to a subject who is known to be at risk of cancer
or is diagnosed
with cancer, an agent for preventative clustering of portions
of cell surface receptors
that,interact with an activating ligand such as a growth factor. . .

36 The method of claim 3 1, wherein the cancer is selected from the group consisting ofe breast, prostate, lung ovarian, colorectal, and brain cancer.

84 A peptide species as in claim 68, wherein the fragment comprises at least a fragment of the sequence that corresponds. . . I that interacts with an activating ligand such as a growth factor to promote cell proliferation in association with MUC I -dependent tumorigenesis.

. remains attached to the cell surface after shedding of the cell surface receptor interchain binding region in association with MUC I -dependent tumorigenesis such that a biornolecule that interacts with that portion of WC I that remains attached to the cell surface after shedding of the cell surface receptor interchain binding region in association with MUC I -dependent tumorigenesis interacts with the fragment.

. in claim 109, wherein the synthetic drug is a derivative of etomoxir.
113. A method for treating a subject having a cancer characterized by the aberrant expression of MUC1, comprising:
administering to the subject ftisaric acid in an amount effective to reduce tumor growth.
114. A method as in claim 1 13, wherein the subject is otherwise free of symptoms calling for treatment with calcimycin.
115. A. . . levels of shed interchain binding region are reduced relative to a control sample.
119. A method for treating a subject having a cancer characterized by the aberrant expression of WC I, comprising:
administering to the subject etomoxir in an amount effective to reduce tumor growth.
120. A method as in claim 119, wherein the subject is otherwise free of symptoms calling for treatment with etomoxin
121. A method. . . levels of shed interchain binding region are reduced relative to a control sample.
125. A method for treating a subject having a cancer characterized by the aberrant expression of MUC I, comprising:
administering to the subject L-(x-methyl-dopa in an amount effective to reduce 1 5 tumor growth.
126. A method as in claim 125, wherein the subject is otherwise free of symptoms calling for treatment with L-(x-methyl-dopa.
127. A. . . levels of shed interchain binding region are reduced relative to a control sample.
131. A method for treating a subject having a cancer characterized by the aberrant expression of WC 1, comprising:
administering to the subject calcimycin in an amount effective to reduce tumor growth.

132. A method as in claim 13 1, wherein the subject is otherwise free of symptoms
calling for treatment with calcimycin.
133. A. . . levels of shed interchain binding region are
reduced relative to a control sample.
137. A method for treating a subject having a cancer
characterized by the aberrant
expression of WC I, comprising:
administering to the subject butylindazole in an amount effective to reduce tumor
growth.
138. A method as in claim 137, wherein the subject is otherwise free of symptoms
calling for treatment with butylindazole.
. A method. . . levels of shed interchain binding region are
reduced relative to a control sample.
143. A method for treating a subject having a cancer
characterized by the aberrant
expression of MUC 1, comprising:
administering to the subject NS 1 619 in an amount effective to reduce tumor
growth.
144. A method as in claim 143, wherein the subject is otherwise free of symptoms
calling for treatment with NS 1619.
145. A. . . composition and the biomolecule; and
determining disruption of the interaction by the candidate drug.
150. A method of treating a subject having cancer or at risk
for developing cancer
comprising:
administering to the subject an agent that reduces cleavage of a cell surface
receptor.
151. A method of treating a subject having cancer or at risk
for developing cancer
comprising:
administering to the subject an agent that reduces cleavage of a cell surface
receptor interchain binding region from the cell surface.
152. The. . . -
corresponds to amino acids 1085 through 1109 of Genbank accession # PI5941, PID
G547937).
156. The method of claim 150, wherein the cancer is selected from the group
consisting of. breast, prostate, lung ovarian, colorectal, and brain cancer.
157. The method of claim 150, wherein the cancer is
characterized by the aberrant
expression of the WC I receptor.
158. A method comprising:
determining an amount of cleavage of a cell surface receptor interchain binding
region from a cell surface; and
evaluating indication of cancer or potential for
cancer based upon the determining
step.
159. A method as in claim 158, wherein the cell surface receptor is MUCL
160. A method as in claim 158, comprising diagnosing cancer in a subject by
determining an amount of shed cell surface receptor interchain binding region in a
subject sample; and
evaluating indication of cancer or potential for
cancer based upon the determining

step.
161. A method as in claim 158, wherein the evaluating step comprises correlating the
amount in a sample to an wriount in a control as an indication of cancer or potential for
cancer.
. A method as in claim 158, comprising:
determining an amount of cell surface receptor interchain binding region at the
surface of a cell from a subject; and
evaluating indication of cancer or potential for
cancer based upon the deten-nining
step.
163. The method of claim 158, wherein the interchain binding region comprises a
contiguous amino acid sequence of. . . 160, wherein the sample is a proliferating cell line derived
from a subject's cells.
. The method of claim 158, wherein the cancer is characterized by aberrant
expression of MUC I.
171. The method of claim 158, wherein the amount of interchain binding region is
determined. . . by a method selected from the group consisting of MALDI, western blotting,
PCR, LCR, rtPCR, cycling probe technology, gel electrophoresis, or antibody-based
assay, magnetic cell sorting, flourescence activated cell sorting, bead-based assays or an
ELISA assay.
172. The method of claim 158, wherein the amount. . . method comprising:
determining a site of cleavage of a cell surface receptor in a sample from a
subject; and
evaluating an indication of cancer or potential for
cancer based upon the
determining step.
176. The method of claim 175, wherein the cell surface receptor is MUC I.
177. The method of. . . blood.
180. The method of claim 175, wherein the sample is a tissue sample.
181. The method of claim 175, wherein the cancer is selected from the group
consisting of. breast, prostate, lung, ovarian, colorectal, and brain cancer.
182. A method as in claim 175, wherein the cancer is characterized by the aberrant
expression of WC I.
183. The method of claim 175, wherein the site of cleavage is determined. . . a
method selected from the group consisting of MALDI, western blotting, PCR, LCR,
1 5. rtPCR, cycling probe technology, gel electrophoresis, or antibody-based assay, magnetic
cell sorting, floureseence activated cell sorting, bead-based assays or an ELISA assay.
184. The method of claim 175, wherein the. . . of claim 185, wherein the surface cell receptor is WC I.
187. A method of diagnosing a physiological state indicative of cancer or potential for
cancer, comprising determining a specific cleavage state of WC I distinguishable from
a different cleavage state of WC1.
. A method comprising:

determining a. . . 188, comprising comparing the first amount to the second
amount as an indication of progression of and/or effectiveness of treatment for cancer.
190. A method as in claim 188, comprising comparing the first amount to the second
amount as an indication for administration of an agent for prevention of cancer.
191. A method as in claim 188, wherein the subject is undergoing treatment for
cancer, the method comprising
comparing the first amount to the second amount as an indication of effectiveness
of the treatment.
192. Amethodasinclaiml88,whereinthecellsurfacereceptorisWC1.
193. The method. . . method of claim 188, wherein the sample is a tissue sample.
I 0 199. The method of claim 188, wherein the cancer is selected from the group
consisting of. breast, prostate, lung, ovarian, colorectal, and brain cancer.
. . .
by a method selected from the group consisting of MALDI, western blotting,
PCR, LCR, rtPCR, cycling probe technology, gel electrophoresis, or antibody-based
assay, magnetic cell sorting, flourescence activated cell sorting, bead-based assays or an
ELISA assay.
202. The method of claim 188, wherein the amount. . .

=>

---Logging off of STN---

=>
Executing the logoff script...

=> LOG Y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	14.60	23.28

STN INTERNATIONAL LOGOFF AT 14:43:49 ON 13 JUN 2006